

What is claimed:

1. A method for modulating the production of A β 11-40/42 peptide fragments comprising contacting a sample or cell containing a beta-site APP-cleaving enzyme 1 (BACE1) and an amyloid precursor protein (APP) with a BACE1-modulating agent such that production of A β 11-40/42 is modulated.
2. The method of claim 1, wherein the modulation is inhibition of A β 11-40/42 peptide formation.
3. The method of claim 1, wherein the contacting is *in vivo*.
4. The method of claim 1, wherein the contacting is *in vitro*.
5. The method of claim 1 wherein the BACE1-modulating agent is an anti-BACE1 antibody or a BACE1 antisense molecule.
6. A method for identifying a compound which inhibits beta-site APP-cleaving enzyme 1 (BACE1) expression or activity comprising:
 - a) incubating components comprising the compound, BACE1 polynucleotide or polypeptide, and an amyloid precursor protein (APP) under conditions sufficient to allow the components to interact; and
 - b) measuring the production of a BACE1 specific enzymatic product.
7. The method of claim 6, wherein the compound is a peptide.
8. The method of claim 6, wherein the compound is a small molecule inhibitor.
9. The method of claim 6, wherein the BACE1 polynucleotide or polypeptide is expressed in a cell.
10. The method of claim 6, wherein the BACE1 specific enzymatic product includes a sequence of A β 11-40/42.

11. A compound identified by the method of claim 6.
12. The compound of claim 11, in a pharmaceutically acceptable carrier.
- 5 13. A method for diagnosing a subject having or at risk of having an A β 11-40/42 peptide accumulation disease, the method comprising:
- measuring the amount of beta-site APP-cleaving enzyme 1 (BACE1) in a biological sample from the subject;
- comparing the amount BACE1 with a normal standard value of BACE1, wherein a
10 difference between the measured amount and the normal sample or standard value provides an indication of the diagnosis of A β 11-40/42.
14. The method of claim 13, wherein the biological sample is blood, serum, cerebrospinal fluid or central nervous system (CNS) tissue.
- 15 15. The method of claim 13, wherein the difference is an increase in BACE1.
16. The method of claim 13, wherein the amount BACE1 is measured by detecting the amount of a polynucleotide encoding BACE1.
- 20 17. The method of claim 16, wherein the polynucleotide is mRNA.
18. The method of claim 17, wherein the mRNA is detected by PCR.
- 25 19. The method of claim 13, wherein the amount of BACE1 is detected by contacting the sample with an agent that specifically binds to a BACE1 polypeptide.
20. The method of claim 19, wherein the agent is an antibody.
- 30 21. The method of claim 20, wherein the antibody is a monoclonal antibody.
22. The method of claim 20, wherein the antibody is a polyclonal antibody.

23. The method of claim 19, wherein the A β 11-40/42 accumulation disease is Alzheimer's Disease.

24. The method of claim 13, further comprising detecting the level of an APP fragment,
5 wherein an increase in the presence of the fragment is indicative of Alzheimer's Disease.

25. The method of claim 24, wherein the APP fragment is a A β 1-40, A β 1-42, A β 11-40, or A β 11-42 fragment.

10 26. The method of claim 25, wherein the fragments are detected by contacting the sample with an agent the specifically binds to A β 1-40, A β 1-42, A β 11-40, or A β 11-42 fragment.

27. The method of claim 26, wherein the agent is an antibody.

15 28. The method of claim 20 or 27, wherein the antibody is detectably labeled.

29. The method of claim 28, wherein the detectable label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

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30. A method for diagnosing a subject having or at risk of having Alzheimer's Disease, the method comprising:

measuring A β 11-40/42 in a biological sample from the subject;

comparing the amount of A β 11-40/42 with a normal sample or standard value of

25 A β 11-40/42, wherein a difference between the amount in the normal sample or standard value is indicative of a subject having or at risk of having Alzheimer's disease.

31. The method of claim 30, wherein the biological sample is cerebrospinal fluid, central nervous system (CNS) tissue, serum or blood.

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32. The method of claim 30, wherein the difference is an increase in A β 11-40/42 and the increase is indicative of a disposition for Alzheimer's disease.

33. The method of claim 30, wherein the difference is a decrease in A β 11-40/42.
34. The method of claim 30, wherein the amount of A β 11-40/42 is detected by contacting the sample with an agent that specifically binds to A β 11-40/42.
- 5 35. The method of claim 34, wherein the agent is an antibody.
36. The method of claim 35, wherein the antibody is a monoclonal antibody.
- 10 37. The method of claim 35, wherein the antibody is a polyclonal antibody.
38. The method of claim 34, wherein the agent is an antibody fragment.
39. The method of claim 30, further comprising detecting the level of a BACE1
15 polypeptide or polynucleotide, wherein an increase in the level of BACE1 is indicative of Alzheimer's Disease.
40. The method of claim 35, wherein the antibody is detectably labeled.
- 20 41. The method of claim 40, wherein the detectable label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.
42. A transgenic non-human animal having a transgene disrupting expression of BACE1,
25 chromsomally integrated into the germ cells of the animal, and have a phenotype of reduced A β peptide as compared with a wild-type animal.
43. The transgenic non-human animal of claim 42, wherein the animal is selected from the group of species consisting of avian, bovine, ovine, piscine, murine, and porcine.
- 30 44. The transgenic non-human animal of claim 42, wherein the animal is heterozygous or homozygous for the disruption.

45. The transgenic non-human animal of claim 42, wherein the transgene comprises a BACE1 antisense polynucleotide.

46. A method for producing a transgenic non-human animal having a phenotype
5 characterized by reduced expression of BACE1 polypeptide, the method comprising:

(a) introducing at least one transgene into a zygote of an animal, the transgene(s) comprising a DNA construct encoding a selectable marker,

(b) transplanting the zygote into a pseudopregnant animal,

(c) allowing the zygote to develop to term, and

10 (d) identifying at least one transgenic offspring whose genome comprises a disruption of the endogenous BACE1 polynucleotide sequence by the transgene.

47. The method of claim 46, wherein the introducing of the transgene into the embryo is by introducing an embryonic stem cell containing the transgene into the embryo.

15 48. The method of claim 46, wherein the transgenic non-human animal is heterozygous or homozygous for the disruption.

49. The method of claim 46, wherein the introducing of the transgene into the embryo is
20 by infecting the embryo with a retrovirus containing the transgene.

50. A method for identifying an agent that modulates the expression or activity of BACE1, said method comprising:

administering an agent to be tested to an organism; and

25 comparing the phenotype of the organism contacted with the agent with that of a BACE1-knockout organism not contacted with the agent, whereby a phenotype substantially equal to the BACE1-knockout organism is indicative of an agent that modulates BACE1 expression or activity.

30 51. The method of claim 50, wherein the organism is a transgenic organism.

52. The method of claim 51, wherein the transgenic organism is transgenic for overexpression of BACE1; APP expression; A β 1-40, A β 1-42, A β 11-40, A β 11-42 expression; or a combination thereof.

53. The method of claim 50, wherein the expression of BACE1 is detected by measuring the amount of BACE1 polynucleotide in the organism.

5 54. The method of claim 53, wherein the BACE1 polynucleotide is RNA or DNA.

55. The method of claim 54, wherein the RNA is mRNA.

56. The method of claim 50, wherein the activity of BACE1 is detected by measuring
10 BACE1 cleavage of APP.

57. The method of claim 50, wherein the phenotype of the organism is associated with Alzheimer's Disease.

15 58. The method of claim 57, wherein the Alzheimer's-associated phenotype is characterized as having a phenotype of impaired performance on memory learning tests and abnormal neuropathology in a cortico-limbic region of the brain.

59. A method for screening for an agent, which ameliorates symptoms of Alzheimer's
20 disease, said method comprising:
comparing an effect of an agent on an organism contacted with the agent with that of a BACE1-knockout organism not contacted with the agent, wherein the organism has a phenotype associated with Alzheimer's Disease and wherein an agent which ameliorates said phenotype is identified by having a substantially equal or superior phenotype of the organism
25 in comparison with the BACE1-knockout organism.

60. The method of claim 59, wherein the phenotype of the organism is characterized as having a phenotype of impaired performance on memory learning tests and abnormal neuropathology in a cortico-limbic region of the brain.

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61. The method of claim 59, wherein the organism is a transgenic organism.

62. The method of claim 59, wherein the phenotype is measured by assessing an organism's performance on memory and learning tests.

63. The method of claim 59, wherein the phenotype is measured by assessing the neuropathology in a cortico-limbic region of the brain.

5 64. A method for screening for an agent, which ameliorates symptoms of Alzheimer's disease, said method comprising:

comparing an effect of an agent on a transgenic organism contacted with the agent with that of a BACE1-knockout organism not contacted with the agent, wherein the transgenic organism is characterized as having a phenotype of impaired performance on
10 memory learning tests or abnormal neuropathology in a cortico-limbic region of the brain and the BACE1-knockout organism has a phenotype of reduced expression of BACE1, wherein the impaired performance and the abnormal neuropathology are compared with the BACE1-knockout organism, whereby an agent which ameliorates the symptoms is identified by substantially equal or superior performance of the transgenic organism as compared with
15 the BACE1-knockout organism on the memory and learning tests.

65. A kit useful for the detection of an A β 11-40/42 accumulation disorder comprising carrier means containing therein one or more containers wherein a first container contains a nucleic acid probe that hybridizes to a nucleic acid sequence BACE1 or an antibody probe
20 specific for BACE1 or A β 11-40/42.

66. The kit of claim 65, wherein the probe is detectably labeled.

67. The kit of claim 65, wherein the label is selected from the group consisting of
25 radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, and an enzyme.

68. A method for predicting the therapeutic effectiveness of a compound for treating Alzheimer's disease in a subject comprising:

30 measuring the accumulation of AB11-40/42 peptide fragments in the subject or the level of BACE1 polynucleotide or polypeptide before and after treatment with the compound, wherein a decrease in accumulation of peptide fragments or a decrease in the level of BACE1 polynucleotide or polypeptide after treatment is indicative of a compound that is effective in treating the disease.

69. A method for monitoring the progression of Alzheimer's disease comprising:
measuring the accumulation of AB11-40/42 peptide fragments in the subject or the level of
BACE1 polynucleotide or polypeptide at a first time point and a second time point, thereby
5 monitoring the progression of the disease.